Essential Tremor: Physiology of Essential Tremor Working Group
Session 3 Document

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The motor system attempts to control the position of body parts either at rest, in posture or during certain tasks. The control problem is difficult with many degrees of freedom of each body part and a complex central nervous system controller. The general description of a controller is that there is a motor command for a certain position, a system to implement the command, and feedback to indicate how well the command is being carried out. Feedback is used to modulate the command if the body part does not have the exact desired position. However, feedback takes time and the interaction of the original command and the feedback information might be complicated. This process may well become unstable; such instabilities are often oscillatory and this would generate tremor.

Since essential tremor is not affected by weighting a body part, it must arise from a central nervous system generator (not a peripheral control loop). Central nervous system generators can be of two types. One would be an unstable loop circuit within the central nervous system, similar to the peripheral loop described earlier. Another would be a nucleus with spontaneous rhythmicity, the spontaneity arising from ion channels in the membrane of the neurons that leads to repetitive depolarizations, generally following hyperpolarizations. A relevant channel in this regard is a low threshold calcium channel found in several central nervous neurons. Such neurons in specific nuclei can participate in recurrent circuits in the brain, so there might be abnormal local rhythmicity that drives an otherwise normal circuit. Both can be true, such that an unstable loop and spontaneous generator can co-exist.

The network hypothesized to relate to the generation of tremor is the cerebello-thalamo-cortical network. There is evidence for cerebellar involvement from various pathological and neuroimaging studies, and this has some face validity given the ataxic features in the patients. There are also reports of strokes in the cerebellum that eradicated essential tremor on the same side (Dupuis *et al.*, 2010). Despite this hypothesis, there remain open questions as to the role of these regions in the action tremor of essential tremor, and the other symptoms of essential tremor. A consistent finding in the literature is that when at rest, patients with essential tremor have elevated blood flow using PET in the cerebellum when compared with control individuals(Wills *et al.*, 1994). However, this study by Wills et al. did not report a difference between groups during the active postural state when tremor occurred, raising questions as to the role of the cerebellum in tremor generation. Neely and colleagues (Neely *et al.*, 2015) studied essential tremor and controls using a force control paradigm that showed enhanced tremor in essential tremor, and found that the BOLD fMRI signal is reduced within cerebellar lobules I-V during force control for essential tremor compared with controls. However, the BOLD fMRI signal did not correlate with tremor between 3-8 Hz, but instead correlated with the 0-3 Hz band of force output. This is consistent with the finding of reduced cerebellar activity in ET patients during finger tapping (Buijink *et al.*, 2015). When TMS was used over the cerebellar cortex, tremor was not reset (Pinto *et al.*, 2003), and inhibitory theta

burst stimulation over the cerebellum did not change clinical tremor severity in ET (Bologna *et al.*, 2015). These studies raise questions as to the causal role of the cerebellum in the generation of tremor.

The VIM nucleus, the cerebellar relay nucleus of the thalamus, contains bursting cells linked linearly to tremor bursts, and these cells burst only when the tremor is present (Hua and Lenz, 2005). A lesion or DBS of the VIM generally reduces the amplitude of the tremor, and injection of muscimol into the VIM suppresses tremor (Pahapill *et al.*, 1999). DBS of VIM additionally leads to increase in tremor frequency (Vaillancourt *et al.*, 2003). Stimulation of the VIM in essential tremor at the tremor frequency can modulate the amplitude of the tremor depending upon the phase of the relationship between the stimulation and the tremor; this suggests a direct relationship to driving the tremor but with an "oscillator" in a narrow range (Cagnan *et al.*, 2014). Transcranial alternating current stimulation (TACS) over the cerebellum can also entrain essential tremor, but again the entrainment is only in a very narrow frequency range (Brittain *et al.*, 2015).

Single pulse transcranial magnetic stimulation (TMS), but not transcranial electrical stimulation (TES) of the primary motor cortex reset essential tremor implicating the importance of intracortical networks in the primary motor cortex (Pascual-Leone *et al.*, 1994). Further, studies using MEG, EEG, and fMRI techniques all suggest that the motor cortex is critical in understanding essential tremor (Hellwig *et al.*, 2003, Neely *et al.*, 2015, Raethjen *et al.*, 2007, Schnitzler *et al.*, 2009).

The cerebello-thalamo-cortical network is also characterized by dysfunctional GABA transmission. Using PET, Boecker and colleagues found increased 11C- flumazenil binding to GABA-A receptors in the ventrolateral thalamus, the dentate nucleus of the cerebellum, and the premotor cortex (Boecker *et al.*, 2010). Whether this is cause or consequence of the tremor remains unclear.

Analysis of motor unit activity in essential tremor shows strong common drive and EEG coherence at the tremor frequency demonstrating a corticospinal drive, but the magnitude of the EEG-EMG coherence does not correlate with the net synaptic input (Gallego *et al.*, 2015). The latter suggests another source for the tremor activity as well. This idea is compatible with the observation that the onset of action tremor precedes significant coherence between thalamic local field potentials and EMG (Pedrosa *et al.*, 2014). Taken together, convincing evidence is lacking that a single brain region drives ET. Instead, different nodes within the cerebello-thalamo-cortical circuit, and possibly altered functional interactions within this circuit (Muthuraman *et al.*, 2012), all appear to contribute to ET.

It might be that in essential tremor the motor controller involving the cerebellum is dysfunctional. The presence of some ataxia is compatible with that idea. Moreover, there is evidence for a delay in motor control processing. Specifically, the second agonist burst in the ballistic movement pattern is delayed (Britton *et al.*, 1994). The delay could set up oscillations in the cerebello-thalamo-cortical loop. Interestingly, and perhaps evidence against this idea, the ataxic component might be separable to some extent from the tremor component in these patients. Ataxic gait, similar to tremor, can improve with DBS, but with supra-therapeutic stimulation there is return of ataxia despite continued improvement of tremor (Fasano *et al.*, 2010). Another issue with this hypothesis is that it is not apparent in this concept where the boundary is between essential tremor and cerebellar tremor. Cerebellar tremor appears to

require a lesion in the cerebellar outflow, and might be a more severe dysfunction of the cerebellar loop than a slight delay. Moreover, it is not even clear that the postural tremor and action tremor of essential tremor is the same. In studies of VIM neuronal activity, action tremor has a lower thalamic spike X EMG coherence than postural tremor (Zakaria *et al.*, 2013).

A possible direct source of cerebellar dysfunction which has been given considerable attention is the input from the inferior olive. The IO is a structure with intrinsic rhythmicity and is involved in the most prominent animal model.

Animal models hold great promise for unlocking the mechanisms of tremor pathophysiology, but the ability of the current models to truly replicate the human condition is not clear. Considerable attention has been paid to the rodent harmaline model of essential tremor. Harmaline is an effective tremorogenic agent in mice, rats, cats, rabbits, monkeys, and even humans (Wilms *et al.*, 1999). Harmaline causes tremor that superficially at least mimics the human condition, and this has served as an accurate model to predict the efficacy of drug treatment. Harmaline increases the oscillations in the inferior olivary nucleus, and this might occur from one of two mechanisms (or both). The olivary neurons are spontaneously rhythmic, the rhythmicity supported by a low threshold calcium channel. The olivary neuron dendrites come together in clusters called glomeruli where they communicate with each other via gap junctions. In harmaline induced tremor, the cells are more rhythmic and they communicate more strongly. Perhaps importantly, the gap junction communication is down-modulated by GABA, so a deficiency of GABA would increase synchronicity. The inferior olivary-cerebellar network has been long suspected as being the relevant generator, but the evidence is largely lacking. A different model in mice occurs with a knock-out of the alpha-1 component of the GABA-A receptor (Kralic *et al.*, 2005). This model could be taken to support one current hypothesis that dysfunctional GABAergic signaling, mainly at the level of the cerebellar nuclei, may be central for tremor pathogenesis in ET (Gironell, 2014). More work is clearly needed. Ideally, the model for essential tremor should be experimentally tractable, measurable, quantifiable, and distinguishable from other motor deficits such as ataxia, dystonia and other forms of tremor that are phenotypically distinct from ET.

What is needed the future

All the issues come together. The definition of essential tremor and what makes up essential tremor, including postural and action tremors, needs to be more definitive. Clinical and physiological studies to separate dystonic tremor and parkinsonian tremor would further clarify the phenotype. This would then allow more definitive pathophysiological studies. More direct neuronal recording in human tremor would be helpful, including correlations at multiple places in the putative network using direct recordings, corticography or EEG. Effects of drugs on these recordings should be useful. It would be good to get more certainty about the pathology and identify some causative genes. Together with the physiology, this would allow the development of more definitive animal models.

Some of this text is taken from (Hallett, 2014).

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